REMARKS

Amendment and Pending Claims

Entry of the amendment to claim 34 is requested under 37 C.F.R. 1.116 to place the claims in better condition for allowance or appeal and to clarify the issues for appeal. Claim 34 is now returned to exactly as it appeared in Applicants' amendment filed February 27, 2006. It would therefore be improper for the Examiner to refuse to enter the amendment to claim 34 on the ground that it presents new issues requiring further consideration and/or search, because the Examiner has already previously considered and examined the language of claim 34. It would also be improper for the Examiner to refuse to enter the amendment to claim 34 on the ground that it presents new matter, because such an action would be a new rejection that would require issuance of a new non-final office action. Claim 45 corresponds to claim 34 as previously presented in the last amendment.

If the amendment is entered, claims 34–42 and 45 are pending and are directed to the treatment of viral infection with a combination of a leflunomide product and a pyrimidine compound. The invention is based on the concept that pyrimidine compounds that supply uridine, cytidine and thymidine (which are the naturally occurring components of DNA) are able to reduce the toxic side effects of leflunomide product without interfering with the anti-viral activity of leflunomide product. See page 20, lines 1-6 of the specification.

Applicants thank Examiner Wang for the courtesy of granting a telephonic interview with the undersigned on December 7, 2006. During the interview, the sole outstanding rejection, relating to written description of pyrimidine compounds "without antiviral activity", was discussed. Possible alternative claim amendments were discussed as well, including a return to the language similar to that of claim 34 as amended on February 27, 2006.

The Outstanding Rejection

The sole outstanding rejection is under 35 U.S.C. §112, first paragraph, on the ground that the recitation of a pyrimidine compound "without antiviral activity" is new matter. All other rejections were withdrawn by the Examiner. Applicants continue to believe that one of ordinary skill in the art would understand from reading the specification that Applicants were in possession of the claimed invention because (a) the purpose of administering the pyrimidine compounds is not for any antiviral effect but rather is to reduce toxicity by supplying uridine, cytidine or thymidine, see page 20, lines 1-6 of the specification, and (b) the application shows in

Example 2, Figure 2 that uridine alone has no antiviral activity. However, because the Examiner indicated during the telephonic interview that Applicants' arguments would not place the claims into condition for allowance, to expedite allowance and clarify issues for appeal, Applicants have amended the claims to return to the previous language of claim 34.

Patentability of the Claims

The prior rejection of claims 34-35 under 35 U.S.C. 103(a) as assertedly unpatentable over Weithmann et al. (U.S. Pat. No. 5,556,870) and Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11) was improper for the following separate and independent reasons, explained previously in Applicants' prior response filed February 27, 2006: (1) the ***failure of the cited art to teach or suggest all claim limitations***, particularly the administration of pyrimidine compounds "in an amount effective to enhance serum levels of uridine, cytidine or thymidine" (see MPEP §§2142 and 2143.03), and (2) **the *unexpected results*** associated with the combination of leflunomide product and pyrimidine compound (which the Examiner was required to consider under MPEP §716.01).

It is axiomatic that the cited art under 35 U.S.C. §103 must teach or suggest ***all the claim limitations***. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a ***reasonable expectation of success***. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. MPEP § 2142. Moreover, MPEP §716.01 states that "Evidence traversing rejections, when timely presented, must be considered by the examiner whenever present. . . . Where the evidence is insufficient to overcome the rejection, the examiner ***must specifically explain why the evidence is insufficient***."

In the Office Action mailed May 23, 2006, the Examiner committed error in (1) failing to show any basis in evidence or scientific reasoning that "administering any compounds having pyrimidine moiety would have reasonably been expected to increase the level metabolites of pyrimidine, such as uridine", (2) ignoring Applicants' evidence and scientific reasoning that such anti-HIV nucleoside analogs do ***not*** enhance serum levels of uridine, cytidine or thymidine, and

(3) ignoring Applicants' evidence and scientific reasoning that administering the anti-HIV nucleoside analogs of Hammer would ***not*** provide the unexpected beneficial effects of the claimed combination (reduction in leflunomide toxicity).

1. Failure to Disclose All Claim Limitations

Hammer, the only reference cited as disclosing pyrimidine compounds, does not disclose all claim limitations because it does not disclose pyrimidine compounds that "enhance serum levels of uridine, cytidine or thymidine" as recited in claim 34 (as amended).

At page 13 of the May 23, 2006 Office Action, the Examiner stated that "administering any compounds having pyrimidine moiety would have reasonably been expected to increase the level [of] metabolites of pyrimidine, such as uridine". That statement is unsupported by any evidence or scientific reasoning, and ignored Applicants' evidence and scientific reasoning that nucleoside analogs cannot supply uridine, cytidine and thymidine, the natural building blocks of DNA.

The nucleoside analogs discussed in Hammer exert their anti-viral effect ***precisely because they are non-natural analogs***. Anti-viral nucleoside analogs inhibit the activity of reverse transcriptase, thereby inhibiting viral DNA synthesis. Thus, the basis for their anti-retroviral activity is their ability to act unlike natural nucleosides, and this anti-retroviral activity is accompanied by toxic effects that are reversible by administration of natural pyrimidines. See Sommadossi et al., Antimicrob. Agents Chemother. 32(7): 997-1001 (1988) and Walker et al., Antivir. Ther. 10 suppl. 2:M117-23 (2005) (abstract) [Exhibits B and C, respectively, to Applicants response filed February 27, 2006], which disclose that uridine can reduce the toxic effects of administering nucleoside analog reverse transcriptase inhibitors.

Thus, the nucleoside analogs of Hammer do not supply uridine, cytidine or thymidine, and do not enhance serum levels of uridine, cytidine or thymidine. During the interview, the Examiner stated his belief for the first time that the term "uridine" broadly encompassed uridine derivatives other than uridine, so that, in his opinion, claim 34 might read on enhanced serum levels of the cited nucleoside analogs of Hammer. Applicants respectfully disagree that "uridine" can be interpreted so broadly. The term "uridine" is understood in the art to refer to a specific chemical compound, and Applicants have nowhere in the specification defined the term "uridine" any differently from its use in the art. See Exhibit I attached (excerpt from Hawley's

Condensed Chemical Dictionary, 1997), which shows that the term "uridine" refers to a specific chemical compound.

Importantly, the Examiner failed to show how Hammer discloses, suggests or motivates one to administer a pyrimidine that *does* "enhance serum levels of uridine, cytidine or thymidine" to treat viral infection, as recited in claim 34 (as amended). Thus, the combination of Hammer with Coghlan and McChesney fails to teach all claim limitations.

2. *Unexpected Results*

The Examiner indicated at page 13 of May 23, 2006 Office Action that he believed that Applicants' unexpected results, i.e. reducing the toxic side effects of leflunomide product, were an inherent property of the cited art. This statement ignored Applicants' evidence and scientific reasoning that administration of the nucleoside analogs of Hammer would ***not*** provide the same beneficial effects, as stated at page 20, lines 1-6 of the specification. In fact, the nucleoside analogs of Hammer themselves cause toxic effects resulting from their interference with normal DNA synthesis. [See Exhibits B and C to Applicants' response filed February 27, 2006]

The Examiner has not provided a reason why the references Coghlan, McChesney and Hammer should be combined, nor has the Examiner shown a reasonable expectation of success that Applicants' claimed combination therapy methods would be successful. As noted in the background of the application, leflunomide product is known to have two mechanisms of action: inhibition of protein tyrosine kinase activity, and inhibition of dihydroorotate dehydrogenase, a key enzyme in the biosynthesis of pyrimidine nucleotide triphosphates. See page 1, lines 17-20 of the background in the specification. The latter activity, inhibition of pyrimidine nucleotide synthesis, leads to reduced pyrimidine nucleotide levels and causes toxicity that that can be reduced by replacing the deficient pyrimidine nucleotides (uridine, cytidine or thymidine).

However, one of ordinary skill in the art would have believed that both of these effects of leflunomide product were necessary for its anti-viral activity, and thus one would have expected that interfering with one of these effects (the reduction in pyrimidine nucleotide levels) would interfere with the anti-viral activity of leflunomide product. Thus, one of ordinary skill in the art would not have expected that co-administration of leflunomide product with a pyrimidine compound that increases serum levels of uridine, cytidine or thymidine would be successful in treating viral infection.

Against this background of the prior art, Applicants' disclosure that increasing serum uridine, cytidine or thymidine levels alleviates toxicity without interfering with the anti-viral activity of leflunomide product is surprising and nonobvious. Example 2 and Figure 2 of the application provided evidence that (a) co-treatment of virus with uridine and leflunomide product ("A77+Ur" in Fig. 2) did not interfere with the anti-viral activity of leflunomide product, and (b) uridine alone ("Ur" in Fig. 2) does not have anti-viral activity.

Evidence confirming these unexpected results is found, e.g., in Chong et al., Transplantation, 1999 Jul 15;68(1):100-9 [Exhibit D to Applicants' response filed February 27, 2006], which states in the abstract that:

> Toxicities associated with high-dose leflunomide (35 mg/kg/day) were anemia, diarrhea, and pathological changes in the small bowel and liver. ***These toxicities were significantly reduced by uridine co-administration***. [Emphasis added.]

WO 2006/014827 [Exhibit E to Applicants' response filed February 27, 2006] shows that another pyrimidine compound, orotic acid, also reduces the toxic side effects of leflunomide.

During the telephonic interview, the Examiner raised new issues of perceived undue breadth of the term "pyrimidine compound". The Examiner is advised that any new rejections of the term "pyrimidine compound" for asserted lack of enablement or written description for the breadth of the term pyrimidine compound would necessitate a withdrawal of finality and issuance of a new, non-final office action. During the interview, it was discussed with the Examiner that a chemist of ordinary skill in the art can easily prepare a number of esters or salts of uridine, cytidine or thymidine, or other intermediates in the body's synthesis of pyrimidine nucleotides such as orotic acid, that can deliver uridine, cytidine or thymidine.

CONCLUSION

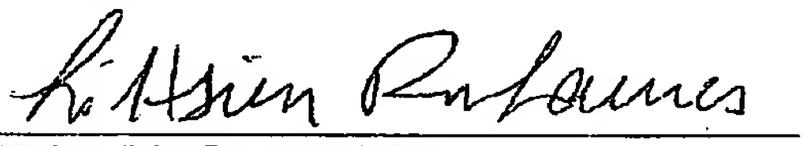
All claims 35-42 and 45 which depend from claim 34 are believed to be patentable for similar reasons. If the Examiner believes that a telephonic interview would expedite prosecution, the Examiner is encouraged to contact the undersigned.

No additional fees are believed to be necessary in connection with the present Amendment. However, the Commissioner is hereby authorized to charge any fees due or deficiency in the fees submitted to our Deposit Account No. 13-2855, under Order No. 28385/35415.

December 7, 2006

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP



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